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Nikola Kirilov Kasabov

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BORSON LAW GROUP, PC
1078 CAROL LANE, #200
LAFAYETTE, CA 94549

EXAMINER

WHALEY, PABLO S

ART UNIT

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1631

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/524,754	Applicant(s) KASABOV ET AL.	
	Examiner PABLO WHALEY	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 8-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 8-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>01/20/2010</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of Claims

Claims 1-6 and 8-23 are currently pending and under consideration.

Claim 7 is cancelled.

Information Disclosure Statement

The information disclosure statement 01/20/2010 has been considered in full.

Withdrawn Rejections

The rejection of claims 1-6 and 8-23 under 35 U.S.C. 103(a) as being unpatentable over Sharpe in view of Kasabov, Kittler, Krogh, and Tsumoto are withdrawn in view of applicant's arguments [p.9] filed 01/20/2010.

NEW GROUNDS OF REJECTIONS

Claim rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Claims 1-6 and 8-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

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invention. Claims that depend directly or indirectly from claim 1, 3, 8, and 23 are also rejected due to said dependence.

The following rejections are newly applied after further consideration.

Claims 1, 3, 8, and 23, Steps ii, iii, and iv, recite the equation: Combined Class A output = $(C1/classA \times \beta1) + (C2/classA + \beta2)$. The claims define C1 and C2 as classified gene expression data and classified clinical information. However, the Specification exemplifies C1 and C2 as prognostic accuracy values [p.19]. Therefore it is unclear whether C1 and C2 represent classified data values or accuracy values

Claims 1, 3, and 8 recite both "Class A" and "classA". There is lack of antecedent basis for "classA." This term is never defined in the claim. The claim defines Class A as a first medical outcome, but it is unclear whether "classA" is the same as Class A or something different. If they are intended to be the same limitation, then it is unclear what the equation for "Combined Class A output" represents since it would then include the data object it seeks to predict or optimize (i.e. class A).

Claims 1, 3, 8, and 23, Steps ii, iii, and iv, recite the equation: Combined Class B output = $(C1/classB \times (1-\beta1)) \times (C2/classB \times (1-\beta2))$ and $(C1/Second\ Class \times (1-\beta1)) \times (C2/Second\ Class \times (1-\beta2))$. As described above, the claims define C1 and C2 as classified gene expression data and classified clinical information. However, the Specification exemplifies C1 and C2 as prognostic accuracy values [p.19]. Therefore it is unclear whether C1 and C2 represent classified data values or accuracy values.

Additionally, it is unclear why the equations $(C1/classB \times (1-\beta1)) \times (C2/classB \times (1-\beta2))$ and $(C1/Second\ Class \times (1-\beta1)) \times (C2/Second\ Class \times (1-\beta2))$ include an "x" representing multiplication of the two terms in parentheses. The specification shows calculating output values for class A and class B using the form $(...) + (...) + (...)$ [See page 20]. Furthermore, the Affidavit filed 02/06/2009 by Nikola Kasabov which provides a detailed discussion of the invention and instead discloses $(C1/classB \times (1-\beta1)) + (C2/classB \times (1-\beta2))$ [See page 3], as supposed to the two terms being multiplied, as in Step iii.

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Therefore it is unclear which equation is intended, one with a "+" or "x" in between the terms? It is noted that this may be a typographical error, and should be of the form $(....) + (....)$, such as in Step ii. However, applicant is notified that if this is NOT a typographical error, then it is new matter. See below.

Claims 1, 3, and 8 recite both "Class B" and "classB". There is lack of antecedent basis for "classB." This term is never defined in the claim. The claim defines Class B as a second medical outcome, but it is unclear whether "classB" is the same as Class B or something different. If they are intended to be the same limitation, then it is unclear what the equation for "Combined Class B output" represents since it would then include the data object it seeks to predict or optimize (i.e. class B).

Claims 1, 3, 8, and 23, Steps ii, iii, and iv, and claims 18 and 21, recite C1/classA, C2/classA, C1/classB, C2/classB, C1/First Class, C2/First Class, C1/Second Class, C2/Second Class, combined Class A/Class B, and combined First Class/Second Class. In each case, it is unclear what operation is intended by the use of "/". For example, Figure 3a shows " $C1 \cap C2$ " which is well known in the field of mathematics and statistics to represent the intersection of two sets, which reads on a combination of two sets. However, the Specification [p.19] also uses the "/" to perform division operations. Therefore it is unclear what limitation of the claimed method is intended by the use of symbol "/", division, intersection, or otherwise. Clarification is requested.

As a result for unclarity of the "/" term, discussed above, it is also unclear what the terms C1/classA, C2/classA, C1/classB, C2/classB, C1/First Class, C2/First Class, C1/Second Class, C2/Second Class represent. The Specification seems to indicate they represent the calculation of weights [p.19]. However, the claims contradict this indication by defining connection weights in Step ii as β_1 , β_2 , and α . It is unclear what classA and class B represent (for reasons discussed above). The claims make reference to the "accuracies" of Class A, Class B, in step iv. Therefore it is unclear whether C1/classA, C2/classA, C1/classB, C2/classB, C1/First Class, C2/First Class, C1/Second Class, C2/Second Class represent values, weights, predictions, accuracies, or something else. Clarification is requested.

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Claims 1, 3, 8, and 23, Step iv, recite the limitation "closer to" which is a relative term that renders the claim indefinite. The term "closer to" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear as to what amount makes a combined Class A/Class B output "closer to 0" or "closer to 1" as opposed to not closer to 0 and not closer to 1.

Claims 1, 3, 8, and 23, Step iv, recite "so that the error...is minimized... and said combined Class A/Class B output has greater accuracy." First, there is lack of antecedent basis for "the error." There is no previous recitation of any error calculation in the claims, only weights and outputs. Second, it is unclear whether applicant intends for this step to be an active method step or not. This could be clarified using ACTIVE language such as "determining an error" and "determining an accuracy."

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

Claims 1-6 and 8-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1 and 3 recite steps for calculating the combined Class B output = $(C1/classB \times (1-\beta1)) \times (C2/classB \times (1-\beta2))$. Claim 23 recites a step for calculating the combined $(C1/Second\ Class \times (1-\beta1)) \times (C2/Second\ Class \times (1-\beta2))$. The specification shows calculating output values for class A and class B

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using the form $(....) + (....)$ [See page 20]. However, neither the specification, drawings, nor claims of the application as originally filed provides support for an equation of the form $(....) \times (....)$. Therefore claims 1, 3, and 23, and claims dependent thereon are rejected for reciting new matter.

LACK OF ENABLEMENT

Claims 1-6 and 8-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. In considering the factors for the instant claims:

a) Quantity of experimentation: The claimed invention is a medical support system that uses classified gene expression and clinical data to predict medical outcomes of a disease or its treatments. The utility asserted by the specification is diagnosis and evaluation of disease [p.1]. The claims are not limited to any particular disease or any particular outcome. In order to practice the claimed invention one of skill in the art must be able to identify classifiers for classifying any gene expression and clinical data; and combine classified gene expression and clinical data to predict an outcome of any disease or any treatment based on the following CALCULATIONS:

Step i) calculating connection weights β_1 , β_2 , and α between Class A and Class B classifier outputs; Step ii) calculating Combined Class A output = $(C1/classA \times \beta_1) + (C2/classA + \beta_2)$ and $(C1/First\ Class \times \beta_1) + (C2/First\ Class + \beta_2)$; Step iii) calculating Combined Class B output = $(C1/classB$

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$\times (1-\beta_1)) \times (C2/classB \times (1-\beta_2))$ and $(C1/Second\ Class \times (1-\beta_1)) \times (C2/Second\ Class \times (1-\beta_2))$; Step iv) calculating Combined Class A/Class B output = (Combined Class A output $\times \alpha$) + (Combined Class B output $\times (1-\alpha)$). For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The amount of direction or guidance presented:

Claims 1, 3, and 23, require combining classified gene expression and classified clinical information to predict an outcome of disease or its treatment. One of skill in the art would not know how this is done for “any” disease or its treatment. The Specification [pages 6-7] explains that an evolving connectionist system using input vectors can combine both gene expression and clinical information by extracting rules that relate the two data sets to obtain personalized treatments. However, the instant claims do not recite any such vectors or rules. The specification is limited to a lymphoma case study [p.17] and does not provide any evidence of specific gene expression data or its relationship to clinical data. Therefore it’s unclear how one of skill in the art would know: (1) what genes correlate with a particular medical outcome; and (2) how to combine classified gene expression data and classified clinical data to predict any disease outcome or its treatment.

Claims 1, 3, and 23 require combining classified gene expression and clinical data to predict an outcome of any disease or any treatment based on the following CALCULATIONS: Step i) calculating connection weights β_1 , β_2 , and α between Class A and Class B classifier outputs; Step ii) calculating Combined Class A output = $(C1/classA \times \beta_1) + (C2/classA \times \beta_2)$ and $(C1/First\ Class \times \beta_1) + (C2/First\ Class \times \beta_2)$; Step iii) calculating Combined Class B output = $(C1/classB \times (1-\beta_1)) \times (C2/classB \times (1-\beta_2))$ and $(C1/Second\ Class \times (1-\beta_1)) \times (C2/Second\ Class \times (1-\beta_2))$; and Step iv) calculating Combined Class A/Class B output = (Combined Class A output $\times \alpha$) + (Combined Class B output $\times (1-\alpha)$).

Regarding Step i), it is not known how the connection weights β_1 , β_2 , and α between Class A and Class B classifier outputs are determined. The Specification [p.19] shows calculating connection weights

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for modules, but not between Class A and Class B classifier outputs to produce a combined Class A/Class B output. The Specification discloses a neural network based system using input nodes, connections, weights, outputs, and distances from rule nodes to establish predictions [pages 8-14]. However, the claims do not recite any limitations directed to nodes and rule nodes.

Regarding the equations of Steps ii) and iii), it is unclear how to perform these calculations for the following reasons. It is unclear what C1, C2, classA, and classB represent (See 112 2nd rejection above). The claims define C1 and C2 as “classified” gene expression data and classified clinical information. However, the Specification exemplifies C1 and C2 as prognostic accuracy values [p.19]. Additionally, it is unclear what the terms C1/classA, C2/classA, C1/classB, C2/classB, C1/First Class, C2/First Class, C1/Second Class, C2/Second Class actually represent (See 112 2nd rejection above). The Specification seems to indicate these terms represent the calculation of weights [p.19]. However, the claims contradict this indication by defining connection weights in Step ii as β_1 , β_2 , and α . Furthermore, Figure 3a shows “ $C1 \cap C2$ ” which is well known in the field of mathematics and statistics to represent the intersection of two sets, which reads on a combination of two sets. However, the Specification [p.19] also uses the “/” to perform division operations. For at least these reasons, it is unclear how one of skill in the art could perform these calculation because the terms required by the equations are not defined and/or are defined differently in the specification vs. the claims.

Regarding Step iv), which additionally requires calculating a Combined Class A/Class B output that is minimized so that the error of combined Class A/Class B has greater accuracy than either Class A or Class B, it is unclear how this calculation is to be performed. The specification shows calculating the accuracy of a combined system [p.16-18]. However, the claims do not recite any limitations for determining accuracy.

c) The presence or absence of working examples: Specification provides working examples for determining prediction accuracies using data and classifiers [p.17-18]. However, the claims don't require

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any such steps directed to prediction accuracies. The specification shows calculating connection weights for modules [p.19], calculating the accuracy of classifications of different modules [p.19-20]. However, the specification does not exemplify calculating connection weights between classifier outputs Class A and Class B to produce a Combined Class A/Class B output, as in claims 1, 3, and 23. The Specification merely speculates without evidence that ANY type of classifier/predictor can be used (e.g. neural networks, support vector machines, rule-based systems, decision trees, statistical methods and the like) for practicing the claimed invention. The Specification explains that evolving connectionist (ECOS) strategies can be used to extract rules that associate input variables (i.e. genes) and output variables (i.e. class categories) [p.12-13]. The Speculations speculates without evidence that they have discovered hidden relationships between sets of genes and clinical information previously unidentifiable. No examples are provided that show the use of the equations, as in claims 1, 3, and 23, for calculating relationship between classified gene expression data and classified clinical information.

d) The nature of the invention: The nature of the invention, prediction of medical outcomes based on gene expression data and clinical information, is complex.

e) The state of the prior art: One of skill in the art, after reading the specification, would not know how to perform the calculations required by claims 1, 3, and 23, Steps i)-iv). The specification does not provide experimental evidence that such calculations can be performed to predict the outcome for any disease or its treatments. Neither the prior art nor post-filing art shows the prediction of medical outcomes based on gene expression data and clinical information using the specific equations of claims 1, 3, and 23. Kasabov teaches a neural network module for adaptive decision support. In particular, gene expression data is used as input into the network for classification [p. 23, last ¶, p.24]. Kasabov teaches an adaptive component that represents weights as a summation of nodes and classes [p.8, lines 20-bottom, p.9, lines 1-15], and an evolving fuzzy neural network system (EFuNN). However, Kasabov does not teach any of the calculations required by claims 1, 3, and 23, nor does Kasabov teach minimizing an error of a

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combined Class A/Class B such that the error of combined Class A/Class B has greater accuracy than either Class A or Class B. Shipp teaches a system that uses machine learning techniques, specifically a weighted voting algorithm and support vector system, for classification of patients based on gene expression data in fatal and cured cases [See at least p.69-71]. However, Shipp does not teach any of the specific equations required by claims 1, 3, and 23, and additionally shows evidence of high misclassification rates for predicting the outcome of their chemotherapy treatment.

f) The relative skill of those in the art: The skill of those in the art of prediction of medical outcomes based on gene expression data and clinical information, is complex.

g) The predictability of the art: The predictability of predicting medical outcomes based on gene expression data and clinical information using the equations required by claims 1, 3, and 23 is unknown in the prior art and is not described in the instant specification.

h) The breadth of the claims: The claims are narrow in that they are drawn to a decision support system for combining classified gene expression and clinical information to predict a medical outcome of any disease, using specific equations, yet wherein the relationship between specific classifiers, genes, weights and outcomes has not been established. The skilled practitioner would first turn to the instant specification for guidance in using the claimed invention. However, the specification lacks any evidence for predictably combining classified gene expression and clinical information to predict a medical outcome of any disease by performing the calculations required by claims 1, 3, and 23. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not teach predictably combining classified gene expression and clinical information to predict a medical outcome of any disease by performing the calculations required by claims 1, 3, and 23. Finally, said practitioner would turn to trial and error experimentation to determine which classifiers should be used for predictably classifying gene expression and clinical information, and which connections weights should be used for calculating a Combined Class A/Class B that predicts a specific disease with greater accuracy than either

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Class A or Class B. Such amounts to undue experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached between 12pm-8pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pablo S. Whaley

Patent Examiner

Art Unit 1631

/PW/

/Marjorie Moran/

Supervisory Patent Examiner, Art Unit 1631